ASBMB today

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beats from the bench

ALSO INSIDE THIS ISSUE: PUBLIC AFFAIRS

- What happens after Hill Day
- Sequestration
- Reflections on the 100 Meetings Challenge

American Society for Biochemistry and Molecular Biology

ASBMB TODAY ESSAY SERIES:

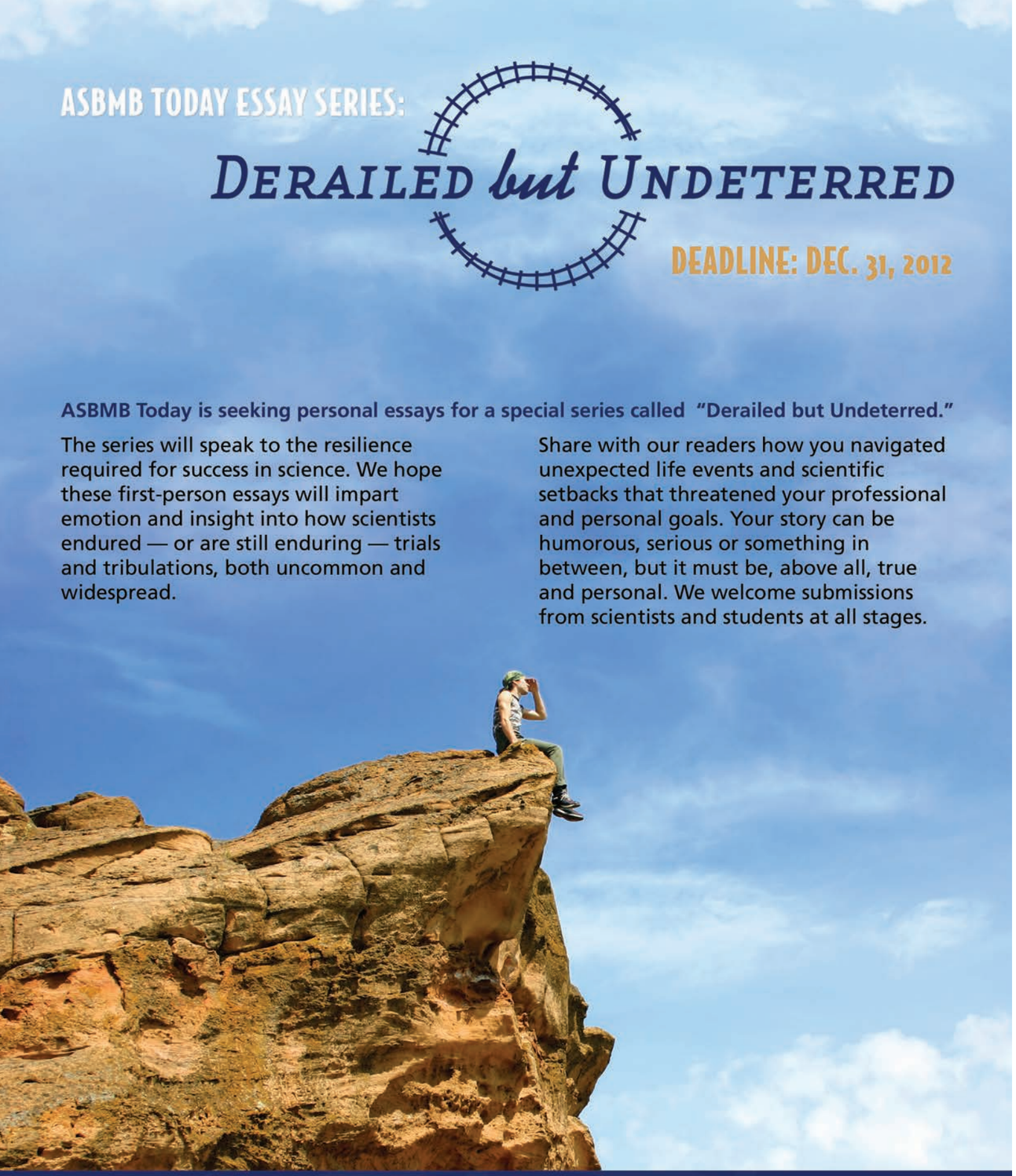
DERAILED *but* UNDETERRED

DEADLINE: DEC. 31, 2012

ASBMB Today is seeking personal essays for a special series called "Derailed but Undeterred."

The series will speak to the resilience required for success in science. We hope these first-person essays will impart emotion and insight into how scientists endured — or are still enduring — trials and tribulations, both uncommon and widespread.

Share with our readers how you navigated unexpected life events and scientific setbacks that threatened your professional and personal goals. Your story can be humorous, serious or something in between, but it must be, above all, true and personal. We welcome submissions from scientists and students at all stages.



Guidelines: *Essays must be unpublished, between 300 and 1,000 words and emailed to asbmbtoday@asbmb.org by Dec. 31, 2012. Please send your manuscript with a brief cover letter, including the title of your submission, complete contact information and an author bio of no more than 100 words.*

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open channels

All atwitter about Nobel Prize in Chemistry

Any time biochemists win the Nobel Prize in Chemistry, chemists start asking what exactly it means to be a chemist. Science writer Rajendrani Mukhopadhyay took a snapshot of how this year's prize to Robert Lefkowitz and Brian Kobilka for G-protein–coupled receptors played out on Twitter.
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Dimensions of diversity

BY JEREMY BERG

We are all shaped by our life experiences. I certainly was influenced strongly by the community in which I grew up. My father was a math professor at Stanford University, and my mother was a physician who worked as a researcher at Stanford Medical School during my early childhood. We lived in a house on the university campus, and I attended an elementary school whose student population was approximately equally divided between children of university faculty and staff members, children of graduate students and children from the surrounding town. On one hand, the school was marvelously diverse, primarily by virtue of the children of graduate students; among about 400 students (grades K–6), between 15 and 20 countries were represented at the annual international day. On the other hand, the school was quite homogeneous. For the majority of students, one or both parents were professionals with advanced degrees. Indeed, it wasn't until I was 12 and started junior high school that I truly realized that the question, "What does your father do?" did not mean, "In what field is your father's master's degree or doctorate?" Most importantly, I had little insight at the time that the world I was experiencing was not the same as that experienced by all other people.

More than 30 years later, I became responsible for a number of programs intended to increase the diversity of the scientific workforce as a component of my position as the director of the National Institute of General Medical Sciences. While I was at the NIGMS, we examined the goals and structures of these programs. Perhaps the most interesting and important discussions that I participated in with National Institutes of Health staff and scientists throughout the United States involved questions of great importance: Why does diversity in the American scientific workforce matter? What are the benefits of a diverse workforce to individuals, to institutions, to the research enterprise, to the nation? Many of the discussion points focused on two major observations that became increasingly apparent during our meetings.

The first observation is that groups with members from highly diverse backgrounds simply perform differently (and usually more effectively) than groups with little diversity. This has been observed empirically in many settings and has been studied more formally as described in Scott Page's book "The Difference: How the Power of Diversity Creates Better Groups, Firms, Schools, and Societies" (1). This observation is certainly consistent with many trends in modern science, such as the interest in interdisciplinary research. Interdisciplinary research teams often have the power to solve hard and important problems because each member of the team brings (at least in principle) a perspective and skill set to the problem that some or all other members of the group may lack.

What does this have to do with dimensions of diversity such as race, ethnicity and sex? At the population level, the reality in our society is that our experiences do depend on these factors. For example, I had a great opportunity to hear from students directly when I attended the 10th anniversary of the Annual Biomedical Research Conference for Minority Students in 2010 (2). This conference attracted more than 2,000 (primarily undergraduate) students from around the country, many of them from black, Hispanic or Native American backgrounds. I learned firsthand how passionate many of these students were about science, despite — or perhaps because of — the fact that they came from backgrounds where interest in a career in research was quite rare.

At this conference, I also presented a keynote lecture. Initially, I was planning to give a talk about the NIH and the programs that the NIH runs to help students — particularly those from groups that have been traditionally underrepresented in science — initiate and progress through careers in biomedical research. However, as I prepared, I wondered how well the audience would connect with what I worried would be a hackneyed talk about bureaucracy. My wife recently had introduced me to "The Last Lecture" (3). This powerful book was written by Randy Pausch, a leading computing science professor at Carnegie Mellon University who was diagnosed with terminal pancreatic cancer and gave a lecture at CMU entitled "Achieving Your Childhood Dreams." In his lecture (4), which went viral on YouTube (more than 15 million views to date), Pausch described his childhood ambitions and how he achieved many of them through determination, powerful mentorship at key points in his life, and support from his friends and family. I was tremendously moved by the book and video, and I decided to change course, shaping my lecture around the same theme: describing my dreams, how I had been able to achieve some of them (as well as some things that I had never imagined possible), and how there remained other dreams to pursue. Though I enjoyed giving the lecture itself, by far the most gratifying part of the experience was the conversations that I had with a number of seminar participants after the talk. One student, in particular, made comments that still resonate with me today, saying, "A lot of speakers at these meetings talk to us about being minorities. News flash: We know that we are minorities, and we don't really think you have much insight to offer us about that. But your lecture got me thinking about what I really want to achieve in my life."

The diverse perspectives I experienced at the conference changed my views on a range of topics, and I hope that I also was able to influence other people's thinking.

Unfortunately, although considerable progress has been made with regard to sex, the biomedical workforce is not yet representative of American society with regard to race and ethnicity. This is particularly true for university faculty. This has implications with regard to the consequences of implicit biases that we all have but of which we are frequently unaware.

The second major observation is that it is essential that there be diverse role models for the scientists of tomorrow. Many of us have been influenced strongly by particular teachers or other individuals over the courses of our lives. Part of this impact comes from our ability to identify with those individuals and to see ourselves in their shoes. Indeed, the importance of role models is borne out by empirical studies. For example, a recent study (5) examined the performance of male and female students at the Air Force Academy based on the sex of their teachers in 2009. The Air Force Academy was used for this study because the curriculum includes a number of mandatory courses and students are assigned to particular professors randomly, simplifying the analysis considerably. The study revealed a correlation between female students' math performance in introductory courses and having female faculty; there was no such correlation noted among male students. Furthermore, having female professors for introductory classes increased the likelihood that female students would pursue additional math and science courses later in college.

Unfortunately, although considerable progress has been made with regard to sex, the biomedical workforce is not yet representative of American society with regard to race and ethnicity. This is particularly true for university faculty. This has implications with regard to the consequences of implicit biases that we all have but of which

In particular, the success rates for applications from black scientists were statistically significantly lower, even after correcting for other factors, such as institution and publication history.

we are frequently unaware. One can hypothesize that increasing representational balance among faculty could be a key strategy for increasing representation in the broader workforce.

Two other recent studies reveal some additional challenges related to diversity. The first is a study showing that simply changing the name on a résumé from "John" to "Jennifer" on applications for a laboratory manager position resulted in a statistically significant decrease in the rating of the applicant as competent and hirable (6). Previous studies have shown similar influences of indications of racial or ethnic backgrounds in other employment settings. These results presumably reflect the impact of implicit biases that affect our judgments even when we are not aware of them.

The second study is an NIH study that revealed differences in funding success rates among different racial and ethnic groups (7). In particular, the success rates for applications from black scientists were statistically significantly lower, even after correcting for other factors, such as institution and publication history. There are several nonmutually exclusive explanations for these observations, including review bias, either implicit or explicit, and the influence of a range of factors on the characteristics of the applications. These studies highlight some of the challenges we face in the 21st century in trying to achieve representational balance in the scientific community.

Moving forward, I hope that students, faculty and institutions alike can refocus our energies on what we want to achieve together while valuing individual differences. To that end, it will help if we all become more aware of our own biases, just as I learned many years ago that not everyone grows up on a college campus. For a thought-provoking experience, I highly recommend exploring some of your own biases on tests available online (8). Diversity enhances the richness of the fabric of the scientific enterprise, including the questions that are asked and how they are approached. We will all learn from others with different perspectives and skill sets and will be able to contribute our own perspectives to benefit others.

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The ASBMB message

BY CHRIS PICKETT

In early September, 20 graduate students and postdocs from around the nation accompanied 10 members of the American Society for Biochemistry and Molecular Biology Public Affairs Advisory Committee on its fifth semiannual Hill Day. The Hill Day participants had a full schedule, conducting 70 meetings with congressional representatives and their staffs. They had meetings with representatives from 26 states, effectively demonstrating that biomedical research is a national endeavor.

The ASBMB representatives delivered clear and concise messages to their members of Congress and their staffs. Previously, participants asked for increases to the National Institutes of Health budget and discussed legislation relevant to the ASBMB membership. This time, however, they focused on two points: (1) the threat of across-the-board budget cuts and the devastating effects they would have on biomedical research and (2) maintaining the United States' competitive edge over countries that are outpacing its investment in biomedical research.

Taking the message home

Talking to representatives in Washington is an excellent way for the ASBMB to demonstrate the importance of the national biomedical research enterprise, and the students and postdocs who participated in this event were highly effective. But an additional goal of the Hill Day is for the participants to take the ASBMB message and their newfound knowledge and excitement for advocacy home to their family, friends and colleagues.

MILLER

Danny Miller, an M.D./Ph.D. student at the University of Kansas Medical Center and the Stowers Institute for Medical Research, lives in Kansas and works in Missouri. While in Washington, Miller met with representatives from both states, but he wasn't done. After the Hill Day, Miller went home and scheduled appointments with the district offices of U.S. Sen. Pat Roberts, R-Kan., and Rep. Emmanuel Cleaver, D-Mo. "I found that the meetings at home were at a much different pace than in Washington," he said later. "The conversation was much more relaxed, and we enjoyed some back and forth about the issues. It gave me time to put a much more personal frame around the conversation."

COLEMAN

David Coleman, a graduate student from Louisiana State University Health–Shreveport, and Melissa Branham–O'Connor, a postdoc at the Medical University of South Carolina, both went home to encourage their colleagues to get involved. Branham–O'Connor was clearly energized by the Hill Day: "As scientists, we should all be concerned with NIH funding, and in our current economic environment it is even more imperative that we engage as many of our colleagues in actively advocating for (research and development)." Coleman agreed, saying, "This advocacy event was a great experience for me and is something I had underappreciated. I know I will be much more involved and will encourage those around me to be as well."

SNELSON

Corey Snelson, a postdoc at the University of Washington, blogs for the Forum on Science Ethics and Policy, Seattle, and focuses her writing on the intersection between biology and public policy. Snelson blogged about her Hill Day experience, saying, "I left feeling quite excited about the future of biomedical research and found that taking part in some small way in my government to be an empowering and instructional experience. I highly recommend everyone give it a try!"

While the ASBMB can deliver effectively the message about biomedical research to offices here in Washington, it depends on energetic people like those who participate in Hill Day to take that message home. Biomedical research is a national endeavor, and the efforts of the Hill Day participants once they leave Washington demonstrate that advocacy on behalf of biomedical research is too.

Chris Pickett (cpickett@asbmb.org) is the science policy fellow at the ASBMB.

THE 100 MEETINGS CHALLENGE

Tales from the field

BY CHRIS PICKETT

What are you doing to improve how research is conducted in this nation? Yes, flat budgets and the threat of across-the-board cuts have researchers scrambling to find the money to support their work. And yes, the funding environment is causing students and postdoctoral scholars to find work in other fields. And on top of all this, one of the few ways to ease this pain requires a deeply partisan and dysfunctional Congress to come to agreement and increase funding for biomedical research.

But the American Society for Biochemistry and Molecular Biology Office of Public Affairs is not so pessimistic. Why? Because biomedical research is one of the few remaining bastions that receive bipartisan support in these hyperpartisan times. This is why Benjamin Corb, ASBMB director of public affairs, issued the "100 Meetings Challenge." Corb challenged members to schedule 100 meetings during congressional recesses to show Congress that biomedical research is essential for the health and economic viability of our nation.

The ASBMB realizes that the idea of venturing into the realm of politics makes some scientists uneasy. What will you talk about? What will the tone be? Does the office even care? To help answer these questions, we had some of our challenge participants tell us a little bit about their experiences.

Richard Thompson, an associate professor at the University of Maryland School of Medicine, and his colleagues met with several members of the Maryland congressional delegation. Here is an edited excerpt from his take on these meetings:

> *Probably the most important thing is that organizing these meetings was easy: Ultimately, we met with staff or members from five Maryland districts and both senators over two weeks. All the staff people and the three congressmen we met with were very welcoming and eager to listen. The ASBMB was a big help in supplying leave-behind material and talking points as well as a useful video on the etiquette of these meetings. We kept the message simple and found the members and their staffs were interested in biomedical science: We weren't so much selling our point of view as having a conversation.*
>
> *We would strongly urge our colleagues in all states to meet with their representatives and senators at home during recess or when they come to Washington, D.C., for a seminar or conference. The congressional meetings were interesting and took only a little time and effort, and we feel like they had a substantial impact.*

Rafael Alvarez-Gonzalez, an ASBMB member since 1987 and a member of the editorial board for Cancer Investigation, met with a pair of offices in Texas and had this to say about his experience:

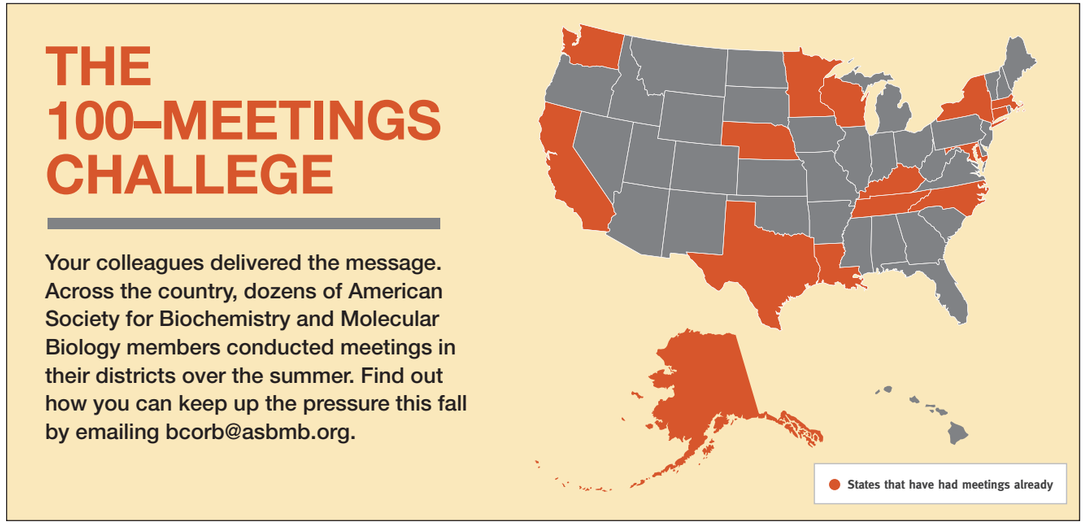
> *A powerful driving force to the long-term success of the ASBMB as a leading scientific society for more than 100 years has been, no doubt, the proactive participation of its members. In my case, I had the privilege of meeting with the honorable Kay Granger and Sen. Kay Bailey Hutchinson, members of the House and Senate Appropriations Subcommittees on Labor, Health and Human Services, Education, and Related Agencies, respectively.*
>
> *To be succinct, the most important point that was underscored in this dialogue was the irreversible negative impact that their decisions might have on the biomedical research community overall … should the (National Institutes of Health) budget be reduced or not adjusted for inflation at the very least — but preferably increased to $32 billion in 2013 and $35 billion by 2015.*

Students and postdocs got involved as well. **Thomas Magaldi,** a postdoc at the National Cancer Institute, told us the following:

> *I immediately jumped at the opportunity to meet with local congressional representatives to advocate for biomedical research funding. However … I feared that Congress did not appreciate the impact of NIH funding on the continued improvement of human health and on the growth of the economy. One 20-minute meeting with Congressman Chris Van Hollen, the top ranking Democrat on the House Budget Committee, helped to alleviate many of my fears. Knowing that representatives such as Congressman Van Hollen are fighting for research funding provided me with optimism over the future of science and technology in the United States.*

A graduate student at the Mayo Graduate School at the Mayo Clinic, **Shirley Dean,** also met with a pair of lawmakers in Minnesota. She reported:

> *The staffer [in the first meeting] appreciated me taking time to meet with them and share my experiences as a researcher. During my second meeting, the staffer was captivated by the issues I raised as I articulated the need for funding increases or at least funding stability that keeps pace with inflation. They saw the passion I had for the sciences and how I and other researchers are working to engage our communities in our research and science in general. This second staffer complimented me for having the audacity to present these issues to them, and I found both of my meetings beneficial for establishing a professional rapport with the politicians who are instrumental in establishing the budgets of government funding organizations.*



Finally, U.S. Sen. Mitch McConnell, R-Ky., is the U.S. Senate minority leader and a well-established fiscal conservative. **Matthew Gentry,** an assistant professor at the University of Kentucky, visited McConnell's office to meet with one of the senator's staffers. He told us this story after his meeting:

> *Simply stated, the entire process was very easy and enjoyable. I expected a 15-minute meeting, but the staffer was quite engaged, and we talked for (about) 45 minutes, which was not a problem, because the ASBMB provided more than enough material. When the staffer left, she commented on the professional appearance of the ASBMB materials, and she said that my preparation of key points and the ASBMB leave-behind materials made her job a lot easier.*
>
> *I came away feeling that my meeting went very well and that the staffer would communicate my views to her boss. I also felt that this meeting, in and of itself, likely will not make a difference. However, if every congressperson is contacted by multiple science advocates, then we will see a difference. She was very willing to listen and pass on my messages, but one voice isn't enough.*

The challenge volunteers have blazed the trail, but it's up to you to take up this mantle. Will you sit at home and hope for the best, or will you get involved and make your voice heard?

Chris Pickett (cpickett@asbmb.org) is the science policy fellow at the ASBMB.

Mayday! Mayday!

BY BENJAMIN W. CORB

One of the remarkable aspects of the biomedical community is its resilience in response to funding obstacles put in place by policymakers in Washington, D.C. Unfortunately, a new fiscal challenge is looming over those who conduct biomedical research: budget cuts the likes of which we have never before experienced. In a field that prides itself on rocking the boat and challenging preconceived ideas of how nature works, these cuts may rock the biomedical research boat too much for the system ever to recover fully.

Last summer, in the midst of an impending fiscal crisis that led to the downgrade of the United States' credit rating, Congress passed legislation intended to slow the rise in federal spending and decrease the national debt. In that legislation, Congress and President Obama agreed to a set of mandatory spending cuts, termed sequestration, amounting to $1 trillion over 10 years. Those cuts would be divided evenly between defense and nondefense spending, the account from which the National Institutes of Health receives its $30.6 billion annual budget. The NIH estimates it will lose $2.5 billion starting Jan. 2, which would eliminate 2,300 new biomedical research grants. That's nearly one-fourth of all new grants.

"It's like a knife hanging over our heads," Bill Chin, executive dean for research at Harvard Medical School,

United for Medical Research, a Washington, D.C.-based coalition, has estimated that the biomedical research enterprise as a whole stands to lose 33,000 scientists and lab workers.

told the Boston Globe last month. "Funding will be reduced for current projects that are working on cures for cancer, Alzheimer's, diabetes and heart disease, all of which have had remarkable advances recently. Ninety percent of our research budget comes from government sources, and the NIH is by far the major source."

In all, sequestration threatens to cut $200 million to $300 million in federal funding for research in 2013 in the Boston area alone. Biomedical research in that region has helped attract a cluster of pharmaceutical companies and biotechnology startups eager to license intellectual property from lab discoveries. Thus, the effects of these staggering cuts to basic biomedical research will have significant repercussions in small biomedical businesses. "Cutting the NIH budget in a weak economy is like jettisoning an engine on an airplane that's losing altitude," Peter Slavin, president of Massachusetts General Hospital, told the Globe.

John Reed, chief executive at the Sanford–Burnham Medical Research Institute in California, said the possible cuts, in the neighborhood of $290 million, in San Diego will be similar to those in Boston. "That size cut is approaching 10 percent of the entire San Diego life-sciences workforce," he told the San Diego Union–Tribune. The number of jobs lost could exceed 4,500 in the San Diego area, with 3,100 of those belonging to scientists and 1,400 to those who support the research industry.

But these are just two regions that are likely to experience devastating consequences should these cuts come to pass. United for Medical Research, a Washington, D.C.-based coalition of research institutions, patient advocacy groups and private industry, has estimated that the biomedical research enterprise as a whole stands to lose 33,000 scientists and lab workers. With these losses to the workforce, it is likely that the current collaborations that exist between labs will become even more competitive and young researchers will choose to abandon biomedical research in search of more lucrative, stable employment.

Mary Hendrix, president and scientific director of Chicago's Children's Memorial Research Center, wrote in a March op-ed in the Chicago Tribune: "Historically, research has fueled job growth and new American industries like biotech, while keeping our nation globally competitive." Hendrix went on to say, "At a time when nations like China and India are rapidly increasing investments in research, America cannot afford to fall behind and lose the jobs and industries that come with medical innovation — not to mention losing an entire generation to lost training opportunities."

In testimony before Congress, NIH Director Francis Collins crystallized the importance of biomedical research to the nation's economy and society. "Biomedical research funded by NIH has prevented immeasurable human suffering and has yielded economic benefits as well, thanks to U.S. citizens living longer, healthier and more productive lives." He continued, "NIH is the leading supporter of basic biomedical research in the world. Put plainly, if we don't fund basic research, most of this work would not get done, and it would be only a matter of time before this wellspring of new understanding and new therapies would dry up." Sequestration, it seems, has the potential to more than just rock the biomedical research boat: It has the potential to sink it.

As dramatic as the cuts could be, it is still possible they will be avoided. Congress, upon returning from an election-season hiatus, has time this month and in December to pass legislation to ease the effects of sequestration, if not eliminate the threat altogether. But the scientific community must have its message heard — and heard loudly — that these cuts are irresponsible and the damage resulting from them irreparable. We need to tell Congress that it can't fix decades of negligent spending by crippling biomedical research. In December, the American Society for Biochemistry and Molecular Biology's Public Affairs Advisory Committee will be calling on you all to have your voices heard in a coordinated fashion, making it impossible for the concerns of the scientific community to be ignored by our nation's leaders and defending the future of America place as a global leader in innovation and research.

Benjamin W. Corb (bcorb@asbmb.org) is director of public affairs at ASBMB.

Lefkowitz, Kobilka claim Nobel Prize for GPCR work

Robert J. Lefkowitz of Duke University Medical Center and Brian K. Kobilka of the Stanford University School of Medicine won last month the Nobel Prize in Chemistry for their studies of G-protein–coupled receptors. Their early work partially explained how cells sense and react to chemical messages, which provided the basis for about 40 percent of today's drugs. More recently, in a feat called a "molecular masterpiece" by the Royal Swedish Academy of Sciences, Kobilka captured visually the moment a hormone triggered a receptor to activate a G protein. "I hope I can continue doing what I'm doing, and I hope that this recognition will positively influence support for basic research," Kobilka noted. In a phone interview with NobelPrize.org, Lefkowitz said he sensed "a tremendous sense of institutional pride" at Duke, for which this is the first Nobel. He continued, "The Nobel prize is often seen, of course, as awards to individuals, but beyond that they're recognition of a field, and so everybody in the field feels good about it." Lefkowitz was the first winner of the American Society for Biochemistry and Molecular Biology's Herbert Tabor Lectureship back in 2004. Kobilka, winner of the ASBMB's most recent Earl and Thressa Stadtman Distinguished Scientist Award, will give an award lecture at the annual meeting in Boston in April.

LEFKOWITZ

KOBILKA

CRESSWELL

WEISS

ATKINSON

Meritorious Career Award. The award given to Cresswell, who recently joined the ranks of the Journal of Biological Chemistry's associate editors, is given annually to a midcareer scientist for outstanding research contributions. Meanwhile, Arthur Weiss of the University of California, San Francisco, won the Lifetime Achievement Award, the association's highest honor. Cresswell and Weiss are both Howard Hughes Medical Institute investigators. The AAI Award for Human Immunology Research went to John P. Atkinson of Washington University in St. Louis School of Medicine for sustained achievement in research.

Cantley leaves Harvard to lead new cancer center

CANTLEY

Lewis Cantley of Harvard Medical School was tapped to head up the new Cancer Center at Weill Cornell Medical College and New York–Presbyterian Hospital, which is slated to open on the Upper East Side of Manhattan in 2014. As director, Cantley will oversee the cancer center's basic and clinical research operations, a tumor tissue bank, patient care and other facilities. A cell biologist, Cantley in the 1980s discovered the signaling pathway phosphoinositide 3-kinase, which is frequently mutated in cancer, and since then has worked to find new treatments for those with such mutations by characterizing the mechanism by which PI3K is activated and by elucidating its pathways. Cantley has been the director of cancer research at Beth Israel Deaconess Medical Center since 2007. He is also co-founder of Agios Pharmaceuticals and serves on multiple scientific advisory boards.

Case Western's Weiss lauded for commercialization, leadership

Michael A. Weiss of the Case Western Reserve University School of Medicine won the Mt. Sinai Health Care Foundation's Maurice Saltzman Award. The award, established in 1983 in honor of a successful businessman and philanthropist who generously supported the Mt. Sinai Medical Center and served on its board of directors, is bestowed annually upon people and organizations that make important contributions to the health interests of the community. Weiss was among 36 nominees. The founder of Thermalin Diabetes and co-founder of Great Lakes Pharmaceuticals, Weiss focuses primarily on molecular endocrinology and has been a major player at the Cleveland Center for Membrane and Structural Biology, a collaboration between scientists and clinicians at Case Western and the Cleveland Clinic, and an important force in the establishment of the Institute for Therapeutic Protein Engineering at Case Western.

Amezquita, Wardlow named HHMI Gilliam Fellows

AMEZQUITA

WARDLOW

Robert Amezquita, a Ph.D. student at Yale University, and Robert Wardlow, an M.D./Ph.D. student at the Johns Hopkins University School of Medicine, both won the Howard Hughes Medical Institute's 2012 Gilliam Fellowships for Advanced Study. Amezquita, a native of San Diego, and Wardlow, a native of Cherry Hill, N.J., were among nine winners of the fellowships, which support underrepresented investigators for five years while they pursue their doctorates. All Gilliam fellows are former participants in HHMI's Exceptional Research Opportunities Program, which matches undergrads with HHMI investigators.

UC-Berkeley's Bustamante wins Vilcek Prize

BUSTAMANTE

Carlos J. Bustamante of the University of California, Berkeley, earlier this year won the 2012 Vilcek Prize in Biomedical Science from the Vilcek Foundation for his single-molecule manipulation methods. The prize honors people born abroad who make important contributions to American society through biomedical research and the arts or humanities. Bustamante, a biophysicist native to Peru, today is director of the Advanced Microscopy Department of the Physical Biosciences Division of the Lawrence Berkeley National Laboratory. The prize includes a $100,000 award and a sculpture.

Immunology society honors Cresswell, Weiss, Atkinson

Three ASBMB members earlier this year won awards from the American Association of Immunologists. Peter Cresswell of the Yale School of Medicine won the AAI-Life Technologies

Palazzo named UAB interim dean

PALAZZO

Currently on leave from Rensselaer Polytechnic Institute, Robert E. Palazzo is now serving as the interim dean for the College of Arts and Sciences at the University of Alabama at Birmingham. The college, created after an academic realignment in 2009, includes programs in the arts, humanities and sciences. Palazzo, a professor since 2002 and a former provost at Rensselaer in Troy, N.Y., was selected for the UAB post for "his extensive experience as an educator, researcher, leader and mentor," the university said in a statement, adding that he had "the best combination of qualities needed" to direct the college during its transition.

ASBMB becomes the U.S. adhering body to IUBMB; Petsko takes reins

BY LOLA OLUFEMI

This fall, scientists from the international biochemistry and molecular biology community gathered in Spain for the 22nd International Union of Biochemistry and Molecular Biology Congress, at which the American Society for Biochemistry and Molecular Biology was made the U.S. adhering body of the IUBMB and former ASBMB President Gregory Petsko became president of the IUBMB. Petsko was elected three years ago and served as president-elect under President Angelo Azzi until September, when his own three-year term began.

PETSKO

Founded in 1955, the IUBMB consists of molecular biologists and biochemists from more than 70 countries, united with a mission to "advance the international molecular life science community." In alignment with the goals of the ASBMB, the IUBMB has endeavored to achieve this mission by promoting diversity, creating networks of scientists that transcend boundaries, developing opportunities for young scientists to excel and promoting an environment where scientific progress is unhindered.

Azzi explains that the role of the IUBMB is to function as "a global organization, trying not to compete with the local societies, but instead trying to represent the world extension of these organizations."

Petsko says he anticipates that this partnership will "provide a forum where investigators can meet their counterparts from other countries and have broader international recognition for their work." He said he also believes this will "enable people who are interested in helping the growth of science in underdeveloped nations to participate in activities that can really make an impact."

This partnership seems natural, as both the IUBMB and the ASBMB previously have collaborated on initiatives that facilitate the progress of the international scientific community. In alliance with the Pan-American Association for Biochemistry and Molecular Biology, the IUBMB and the ASBMB developed a training program that offers young scientists active in the PABMB an opportunity to perform novel research in the laboratories of ASBMB-affiliated scientists. That program is called Promoting Research Opportunities for Latin American Biochemists, or PROLAB.

Azzi says he hopes that the partnership between the ASBMB and the IUBMB will continue to birth similar programs that will facilitate the growth of scientists at all stages, particularly those in developing nations, adding that he expects "the innovative mind of Greg Petsko will provide new developments and fresh ideas for (the IUBMB) especially to the benefit of scientists who have been less fortunate."

Petsko admits that fostering the growth of scientists in developing countries is the challenge he will "need to come to grips with during the next three years" and says that he is planning to work in close partnership with the ASBMB leadership to develop structured initiatives. Petsko says his immediate goals for the IUBMB include an "increased focus on the role of women and minorities in the affairs of IUBMB, increased emphasis on educational activities, and the continuation of the educational and outreach activities that were begun so ably by Angelo during his term in office."

In the long run, Petsko says, he is interested in exploring new ways for members to communicate, including newsletters, blogs and Twitter. He is also interested in examining "how scientific publishing may be changing from the perspective of our excellent IUBMB journals."

Petsko urges ASBMB members to contribute to these efforts by "remaining a strong vital organization and increasing ASBMB membership, especially of young scientists, women and minorities." He also encourages members of both the IUBMB and the ASBMB to voice their opinions on programs they would like to see implemented.

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Retrospective

George F. Cahill Jr. (1927 – 2012)

BY RICHARD W. HANSON

George F. Cahill Jr., who died July 30 at the age of 85, is remembered as one of the most imaginative scientists ever to have graced the field of metabolism. His obituary in the New York Times (1) and a more formal reflection (2) on his career by C. Ronald Kahn of the Joslin Diabetes Center, Cahill's academic home for the best part of his career, capture the formal aspects of Cahill's contributions to science. Perhaps the publication that most lovingly presents Cahill's life and times, as well as his approach to science, was written by his former fellow and collaborator, the late Oliver E. Owen; it was published in Harvard Medicine (3) and was a favorite of Cahill's.

This article is a more personal reflection on the impact of Cahill's research on the field of metabolism and on the unique and unparalleled insights that it has provided. To understand his contributions to metabolism, it is important to recall a bit of the history of this field during the last half of the 20th century, the period when he worked.

Most of the major advances in metabolism in that era involved the discovery of the pathways of fuel utilization, the key enzymes in these pathways and the factors that control these processes. This was followed by the isolation and characterization of genes that code for major enzymes in metabolism and an understanding of their regulation. This field continues to provide insights into biological processes in general.

Cahill was not a biochemist but a physician–scientist: His approach to research was integrative and not reductionist in nature. One example of this is his early research on the effects of hormones on the metabolism of adipose tissue and liver. In the 1950s, research on the biology of adipose tissue was in its infancy. Before this period, adipose tissue was generally considered to be simply "fat," as it was termed, just a storage site for triglycerides and of only marginal interest in the control of whole-body metabolism.

Cahill and Albert Renold, another physician–scientist, who had worked at Harvard Medical School with the famous Baird Hastings, collaborated on pioneering research on adipose tissue metabolism. In a series of papers in the early 1960s, many of them published in the Journal of Biological Chemistry (4, 5), Cahill and Renold provided a primer on how to study metabolic pathways in

adipose tissue and liver. They also showed how to use this information to understand the effects of hormones, such as insulin and epinephrine, on the metabolism of these tissues.

I began my scientific life as a graduate student during this period and remember well the effect that these publications made on my own career: They taught me how to use isotopic tracers and to isolate the end products of metabolism, such as CO2, glycogen, fatty acids and glyceride-glycerol, from tissues. I would recommend these papers to the new generation scientists interested in metabolism for their clarity of approach and elegance of concept.

It was during this period that Cahill and Renold edited for the American Physiological Society the "Handbook of Physiology: Adipose Tissue," which contained more than 4,000 references and was for many years the bible of adipose tissue metabolism. If he had done nothing more in his scientific career, Cahill would have been remembered as a pioneer for his studies of the metabolism of adipose tissue.

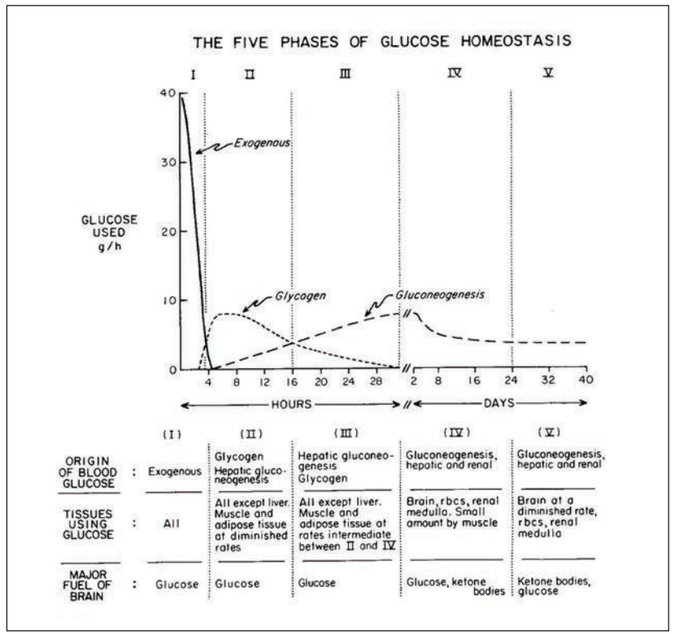

Fig. 1

In 1962, Cahill was named director of what was to become the Joslin Research Laboratories, and he held the position until 1978. It was at the Joslin and in the Clinical Research Center at the associated Peter Bent Brigham Hospital that Cahill and his colleagues carried out the groundbreaking experiments in human metabolism for which he is justly famous. These experiments were described in some detail by his colleague Oliver E. Owen (6), and the reader is directed to that article for the insight that it provides on what it was like to do human experimentation in that era.

The major scientific question that interested Cahill during this period was the metabolic adaptation of humans to starvation. Techniques were available to determine the concentration of metabolic fuels in venous and arterial blood and in the urine in human subjects, and Cahill and colleagues used them to study metabolism during starvation. A major issue was fuel metabolism by the brain. In the early 1960s, it was known that the brain utilized glucose at a rate of 100 to 145 grams per day, but it was widely held that the brain did not oxidize ketone bodies for energy. Ketone bodies are unique as a metabolic fuel, because their concentration can vary from virtually undetectable levels after a meal containing carbohydrate to 7 mM after five weeks of starvation. As Oliver Owen pointed out (6), "Cahill was one of the few clinical investigators at the time to believe that during starvation there was not enough nitrogen in the urine to account for the alleged amount of glucose that the brain was thought to need for normal function."

The link between the excretion of urinary nitrogen and glucose utilization by the brain was a critical insight, because the major source of glucose during starvation is gluconeogenesis from amino acids, a process that generates urea. The brain clearly had to use a fuel other than glucose during starvation to make the numbers add up. This point was experimentally established by directly measuring the utilization of ketone bodies by the brain in subjects starved for five to six weeks by determining the arterial-venous difference in the concentration of ketone bodies across the brain.

The results of these studies were published in the Journal of Clinical Investigation in 1967 (7) and quickly became a "Citation Classic." In the metabolic field, these findings had a major impact, because they provided a basis for understanding the principle of fuel sparing, which occurs in all mammals. The fact that the brain, which normally uses glucose as its fuel of choice, would switch its fuel preference to ketone bodies, which are synthesized from fatty acids in the liver, provided a major insight into the control of energy metabolism. As Cahill pointed out on many occasions, a 70-kilogram human has 141,000 kilocalories of triglyceride and only 900 kilocalories of carbohydrate stored as glycogen, mainly in the liver and skeletal muscle; glycogen in the liver is depleted after about 12 hours of fasting, after which the major source of glucose is gluconeogenesis from amino acids. If tissues such as the brain and skeletal muscle continued to use glucose as a primary fuel, the depletion of muscle protein would be accelerated, greatly impeding our ability to survive a prolonged fast. Thus, the utilization of fatty acids, or fatty acid-derived ketone bodies, is at the heart of fuel sparing. As an example, fatty acids block both glucose uptake and oxidation via glycolysis and the citric acid cycle in skeletal muscle, a major adaptation to fasting.

Cahill and colleagues made another major discovery through research carried out between 1967 and 1971. They reported that alanine and glutamine are the major amino acids released by skeletal muscle of humans during prolonged fasting (8). Alanine is a substrate for hepatic gluconeogenesis, and glutamine is converted to glucose by the kidney cortex; the ammonia generated by this process is used to maintain the neutrality of the tubular urine. The discovery of the unique metabolic role of two amino acids during fasting out of the 20 that make up the protein of skeletal muscle provided another critical contribution to our understanding of the metabolic adaptations that occur during starvation.

Cahill's research is monumental in its scope, as it establishes a framework upon which to understand human metabolism. Like the discovery of the urea and citric acid cycles by Hans Krebs, Cahill's work provides us with a new way of thinking about energy metabolism. Over many years of teaching biochemistry to medical and premed students, I have found that nothing introduces the complexity of metabolism better than to begin with the work of Cahill and colleagues, as it forms a base upon which the interaction of specific metabolic pathways can be structured.

It is of interest that many textbooks of biochemistry include a figure showing the five phases of glucose homeostasis (figure 1) drawn directly from Cahill's work (9). Understanding the metabolic imperatives that form the basis of fuel sparing makes it easier, for example, to understand why elevated levels of free fatty acids in the blood inhibit glucose utilization by skeletal muscle as observed in insulin resistance in humans.

As Carl Sandburg wrote of Abraham Lincoln, "a tree is best measured when it is down." So it is with Cahill.

Cahill lived a productive and very fulfilling life. He was married to Sarah Townsend du Pont, and they had six children and 15 grandchildren. He served in the U.S. Navy from 1945 to 1947, graduated from Yale University in 1949 and received his M.D. from Columbia University in 1953. His long relationship with Harvard University began with his internship and residency at Brigham and Women's Hospital in 1953. He was appointed an assistant professor of medicine at Harvard University School of Medicine in 1962 and remained at Harvard until 1978, when he became director of research at the Howard Hughes Medical Institute. In 1990, he was named professor of biological sciences at Dartmouth College, a position he held until 1998.

Cahill was a very charming and charismatic man, loved and respected by his fellows and colleagues and a delight for his students. I remember being with him at meetings when he would inevitably ask the same question of a speaker who had presented what seemed a rather arcane lecture: "Your lecture was very interesting, but what message can I take back for my medical students?" It was only later in my life that I understood the importance of that question for all of us who teach metabolism. When he retired from Harvard and the Howard Hughes Medical Institute, he moved to his home in New Hampshire and was appointed to the faculty at Dartmouth College. After a year or so of lecturing, his classes were so popular with the students that the college had to move the class to a larger room.

As Carl Sandburg wrote of Abraham Lincoln, "a tree is best measured when it is down." So it is with Cahill. He published more than 350 papers during his career in science, four of which were "Citation Classics," with more than 500 citations each. He was sought after for his contributions to scientific societies and as a consultant to industry and governmental agencies and served on numerous editorial boards for scientific journals;

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Retrospective

Annemarie Weber (1923 – 2012)

BY CLARA FRANZINI–ARMSTRONG

Annemarie Weber was a major contributor to the renaissance of muscle biology research in the 1950s to 1970s, when the components of the contractile machinery were identified; novel views of muscle contraction and regulation were elucidated; and principles of energy transduction, motility and intracellular signaling common to all cells were revealed. While Annemarie was introduced to research by her father, Hans H. Weber, a muscle physiologist, she strode off on her own, establishing her credentials in publications that were innovative, thorough and meticolus. She quickly achieved international scientific recognition and became a dominating figure in the field, a significant feat at a time when developing an independent scientific career was not easy for women.

Annemarie provided direct evidence for the role of calcium ions as intracellular messengers. Some hints already existed: Small amounts of calcium-contaning solution introduced into muscle fibers resulted in localized contractions (1, 2), an indication that calcium could be a physiological activator. However, in vitro experiments with isolated proteins and myofibrils were baffling and gave uncertain results. Before the availability of calcium-specific chelators, calcium was a contaminator of glassware and chemicals. Magnesium added further complication and, at low concentrations of ATP contraction, was calcium-independent, so major skepticism remained on the activator role of calcium.

Annemarie (3) calculated the effect of free calcium ion concentration on various ligands and established that very low concentrations of ionized calcium are uniquely necessary and sufficient to activate the contractile machinery of muscle in the presence of physiological (mM) concentrations of MgATP. She further interacted with the Japanese scientist Setsuro Ebashi, also a supporter of the calcium hypothesis, who had identified the calcium binding and ATPase activity of a vesicular fraction derived from sarcoplasmic reticulum, or SR (4).

Wilhelm Hasselbach (5) demonstrated the ATP-dependent calcium-pumping action of isolated SR, and Annemarie finally demonstrated that SR vesicles could account fully for muscle relaxation via their calcium-sequestering ability (6). Her experiments and calculations were so compelling that they ended years of dispute, eliminating the hypothesis of a soluble relaxing factor. Her insights paved the way for the discovery by Ebashi of a myofibrillar protein with high affinity for calcium, troponin C (7), and led to the subsequent realization that most cells use calcium as an intracellular messenger.

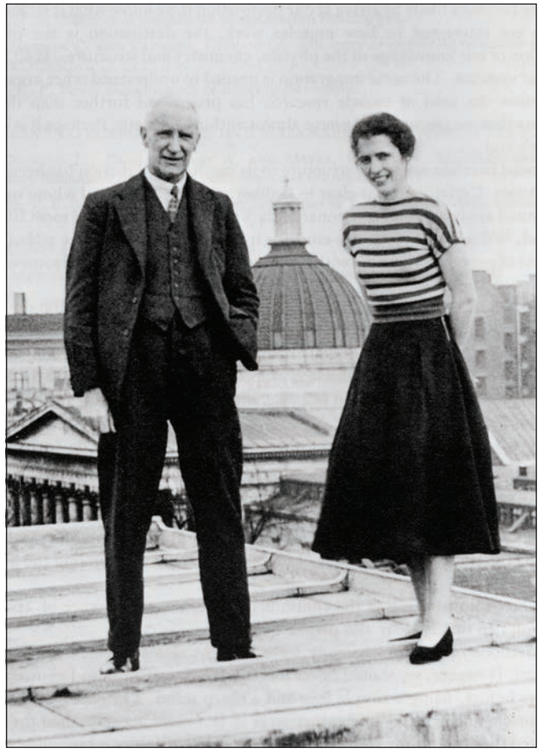

IMAGE CREDIT: J. EXP. BIOL.

A.V. Hill and Annemarie Weber photographed by D.R. Wilkie in 1951 on the roof of the biophysics building at University College London.

The basic mechanisms Annemarie discovered in muscle apply very broadly: The free calcium concentration in the cytoplasm is kept low mostly due to the sequestering action of the endoplasmic reticulum and SR, while cytoplasmic proteins, such as troponin (in muscle) and calmodulin (in other cells), act as second messengers for cellular processes via their high calcium affinity.

Annemarie next directed her attention to the mechanism by which calcium activates contraction. The steric hindrance model (8, 9, 10) suggested that tropomyosin and the troponins, components of the actin-containing thin filaments, act as a complex calcium-sensitive switch for contraction. Annemarie was able to clarify the mystery of the calcium-independent activation of actomyosin interaction at low MgATP concentration by showing that the myosin crossbridges still attached to actin and waiting to bind ATP effectively act as a foot in the door, producing a cooperative activation of seven actin subunits along the thin filament (11). Her work provided an additional graphic picture of the way in which tropomyosin, which covers and inhibits actin subunits at rest, is forced out of the way after calcium binding to troponin C.

The last scientific challenge for Annemarie was to understand the formation and disassembly of actin filaments, which are present in a dynamic state in all eukariotic cells. In collaborative work, Weber used her understanding of kinetic processes to define the the regulation of actin-subunit association and dissociation at the slow-growing (pointed) filament end. She demonstrated that the actions of DNaseI and tropomyosin on that end of the filament are due to their specific effects on the actin subunit off-rate. Subsequently, in nice symmetry to her earlier work, she collaborated with Velia M. Fowler to show that tropomodulin is the long-sought-after capper for the thin filament pointed ends in striated muscle (12, 13). Her original molecular and kinetic insights still form the basis for studies of tropomodulin action.

Annemarie was an incredibly successful teacher, because she was totally dedicated, she had an inexhaustible enthusiasm for the material, and she liked challenging students, colleagues and herself while striving for perfection. Advanced scientists still remember being inspired by attending her famous physiology course at the Marine Biology Laboratory in Woods Hole, Mass. At the University of Pennsylvania, which she joined in 1972, she completely revised the medical biochemistry course with a novel approach, earning the students' enthusiasm and the university's Provost Award for Distinguished Teaching.

To have known Annemarie Weber was an unforgettable experience. My own appreciation started with the initial admiration at her 1964 Federation of American Societies for Experimental Biology meeting presentation, when she shredded the last lingering concepts of a soluble relaxing factor. I read with a sense of discovery her 1972 definition of the cooperative activation of actin filaments: what wonderful intuition! I then shifted into definite panic when I had to talk in her presence at the Pennsylvania Muscle Insitute in Philadelphia. I feared to hear the famous "Look here, sweetie" that preceeded one of her incisive comments on some inconsistency she had noticed in the presentation. I had seen famous scientists shake in their boots when she asked one of her pointed questions.

Later, when I knew her better, I discovered the enormous generosity of her friendship. She was a challenging and stimulating scientifc adviser. She gave me thoughtful insights into my children (who confided in her) and stimulating books covering all sorts of subjects. She took me mountain hiking. She challenged my husband, Clay, in friendly debates. She similarly took care of and stimulated a large network of friends, including her German nephews and nieces and their children, for whom she planned

interesting scientific experiments during their visits to Woods Hole. Her collaborator, Velia Fowler, remembers fondly her rigorous explanations of actin polymerization kinetics in conversations prefaced by the words, "But this is kinetics 101!" while being graciously hosted at her house. Trainees both at Penn and outside were daunted by the challenge of creating experimental designs and generating data that met her approval. Most touching was the fact that she maintained a courageous and cheerful demeanor up to the very last stages of lung cancer to maintain her independence and to hide her suffering from friends and relatives.

Annemarie had a strong personality, an ever-active intellect and boundless generosity. A unique scientist, teacher, mentor and friend, she will be missed.

Acknowledgments
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the list of his service is too long to reproduce here. He won many honors over his lifetime, all related to his groundbreaking work in human metabolism, but oddly he was not elected to either the National Academy of Sciences or the Institute of Medicine. I think that this oversight was due in part to the years in which he did his research – during the transition from an emphasis on metabolism to the revolution in molecular biology and genetics. Also, his research was integrative rather than reductionist: It did not provide information on a new metabolic pathway or the structure of a gene; what it did was change the way we understand human metabolism, and in that way his contributions to science are unique.

As anyone who has worked in science can attest, generating great ideas seems simple in retrospect, but oh so difficult in practice! Few people have contributed more to medicine than George Cahill, and for that he has earned a rightful place among the greats of his discipline.

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the sounds of science

BY JOHN LaCAVA

IMAGE CREDIT: MANON CEDERROTH

Consider for a moment how creative and inspired these ideas are: All matter is fundamentally composed of infinitesimally minute, indivisible particles; the Earth and other planets orbit the sun; organisms too small to be seen with the naked eye can cause horrific disease. Scientific research is demonstrably one of the most imaginative endeavors one can choose as a profession. Yet if you were to pull aside a random person on the street and ask him or her to identify a creative profession, it is doubtful that "scientist" would be the response. But why should the scientist not be recognized as a highly creative professional?

A few years ago, I initiated a science music project called www.soundsofscience.net at The Rockefeller University, executed with the aid of several collaborators on campus and local New York City music producers. As the executive producer, my vision was to provide a mechanism for science to be consumed through art — it was an experiment in the public communication of science through music. Why? Because I imagined most people unfamiliar with scientific research could digest it better in the form of something they found familiar and palatable, not in an esoteric, high-art embodiment, but through conventional songs that get your foot tapping and hips moving – music that stands alone on its merits, in a popular style, while also integrating science.

I could not have been more pleased with the outcome. As you will find on our website, we have been able to produce numerous catchy, trip-hop pieces of music that effortlessly incorporate laboratory sounds and themes. "He is creating/the perfect picture/punching radioactive black holes/into the angelic white," are lyrics from the song "Bubble Up in the Lab 2 w/Vox," sung by Pinar Ayata about her lab mate and the first author of a recent Science paper (1). The song artfully describes experimental techniques used in the paper to identify a crucial nucleotide factor likely involved in epigenetic control of neuronal function. Another song, "96 Tubes," laments the tedium of multiwell experiments (coincidentally, as I write this article, I am temporar-

IMAGE CREDIT: MANON CEDERROTH

IMAGE CREDIT: MANON CEDERROTH

ily situated in Seattle to work on robotic automation of multiwell affinity chromatography experiments). You can hear the science in these songs, but the music stands on its own.

In addition to making music, however, our soundsofscience.net project takes this concept a step further: We also want to influence the creation of music by artists and producers. Having recorded a large library of high-quality source samples from laboratory apparatus and ambiance, we have recently launched what we believe is the first public repository of science and engineering sounds: www.sosdb.net. Our hope is that by showing examples of what can be done musically, by making music that rocks in a club or bar setting, and by providing all the sounds we have recorded for other producers to use, we may be able to seed a science-sounds-based music community, much in the tradition of musique concrète, which has roots stretching back to the 1940s.

There have been other science-related music projects, but none to my knowledge has intentionally incorporated the sounds of real research laboratories or used scientists as musicians in the composition and performance processes. The Large Hadron Collider rap song and the "Bad Project" Lady Gaga rip-off went viral in recent years, but as parodies they are not terribly effective for outreach. Rather, the performers are making fun of themselves, and these productions are geared to be consumed by those already on the inside; though we as scientists laugh at our own nerdiness, most people who don't work in a lab won't find them funny or interesting at all. Symphony of Science is a very well-produced project that has a lot of musical originality and overtly scientific themes mostly based on the old PBS "Cosmos" series. However, even though this project has achieved a high degree of visibility and success, it fails to incorporate real scientific source sounds or diverse musicianship within its essential composition. Another project of note, DarwinTunes, developed at Imperial College London, creates music from otherwise discordant short audio loops, using a genetic algorithm and audience selection (2).

By achieving a significant level of public visibility alongside other notable outreach projects, music, and art in general, can help to associate science with forms that are traditionally considered both creative and culturally viable. These are perceptions that science already rightfully deserves but, due to a variety of social and cultural barriers, still lacks. The more commonplace these hybrid science–art media projects become, the more casually the public will be able to consume scientific motifs, leading to the research culture becoming an established presence in popular culture and helping to usher in an era of basic public awareness and improved general perception of science. It is but one pebble thrown in the vast ocean, but the ripple effect so elegantly described by Christian J. Doppler will slowly but steadily spread, making an impact on every corner of the globe.

RESOURCES

Website: www.soundsofscience.net

Database site: www.sosdb.net

Facebook: www.facebook.com/soundsofscience.net

Twitter: www.twitter.com/sounds_science

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feature*story*

The discovery of essential fatty acids

BY RAJENDRANI MUKHOPADHYAY

George and Mildred Burr upended the notion that fats only contributed calories in the diet

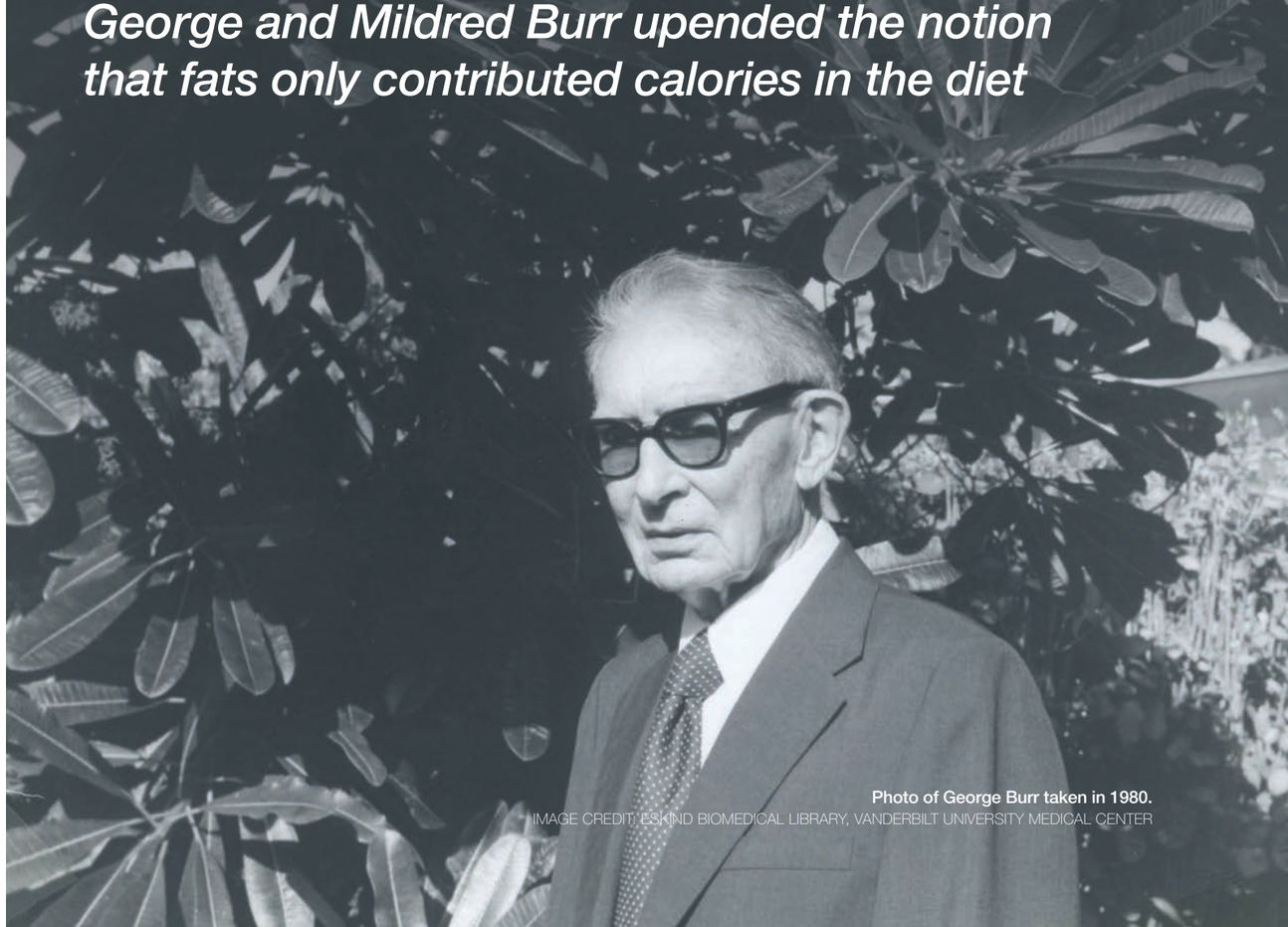

Photo of George Burr taken in 1980.

IMAGE CREDIT: ESKIND BIOMEDICAL LIBRARY, VANDERBILT UNIVERSITY MEDICAL CENTER

In the early 1900s, dietary fat was viewed simply as a source of calories, interchangeable with carbohydrates. But in 1929 and 1930, a husband-and-wife team published two papers in the Journal of Biological Chemistry that turned the notion on its head. Through meticulous analyses of rats fed special diets, George and Mildred Burr discovered that fatty acids were critical to health. If fatty acids were missing in the diet, a deficiency syndrome ensued and often led to death. The Burrs identified linoleic acid as an essential fatty acid and coined the phrase "essential fatty acids."

The work by the Burrs "showed that fats are not there solely as calories to support growth but that they are important for proper physiology," explains Norman Salem Jr. of DSM Nutritional Products, a company that makes bulk vitamins, lipids, carotenoids and other nutrition products. The two papers heralded "the beginning of a modern paradigm in nutritional biochemistry."

The field of nutritional fatty acid research has exploded since the work by the Burrs and now affects our daily lives. Food manufacturers add fatty-acid supplements, such as the omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid (more popularly known as EPA and DHA), to processed foods, and government agencies work to establish guidelines on which fats should be incorporated into healthful diets.

In a speech he gave in 1980 at the Golden Jubilee International Congress on Essential Fatty Acids and Prostaglandins at the University of Minnesota, George Burr recounted how he stumbled into the research project that changed the perception of fats (1). In 1924, as a freshly minted Ph.D. in biochemistry from the University of Minnesota, 28-year-old Burr joined the staff of Herbert Evans at the University of California, Berkeley. Evans already was famous because he, along with Katherine Scott Bishop, had discovered vitamin E two years earlier. Burr joined the laboratory as a research associate and was tasked with understanding the chemistry of the vitamin.

At the time Burr arrived at the Evans laboratory — along with a Gila monster he recently had captured on an Arizona scientific expedition and had had stuffed — his colleagues were grappling with a problem. They were trying to produce sterile female rats as controls for an assay with a diet deficient in vitamin E. But for some reason the rats were not always sterile. It seemed that some lipid component with vitamin E in it kept sneaking into their diet.

To tease out the details, George Burr put a group of rats on a highly purified and simple diet. The diet consisted of sucrose and casein, both of which he and his colleagues repurified after they received them from the manufacturers to make sure there weren't trace components that could somehow affect results. To the sucrose and casein, they added components such as highly purified salts and vitamins. They then fed the concoction to the rats. "In a little while, we had an extreme deficiency in our young animals," Burr said in the 1980 speech. "We had run our first fat-deficiency experiment and didn't know it."

The researchers searched the literature to figure out where they had gone wrong. They had added all the known vitamin supplements to the simple diet, but they were still getting a deficiency syndrome. Burr said in his 1980 speech that nutrition experts of the time insisted to him that fats were not necessary for a complete diet.

As he tried to figure out what was going on with the sick rats, Burr accepted an offer to join the new department of botany at the University of Minnesota. By this time he was married to a technician named Mildred (her maiden name was Lawson) who was responsible for the Evans laboratory's stock rat colony. So that George Burr could start his new post in 1928, the couple left Berkeley, Calif., for Minneapolis in a Model-T Ford with two cages of rats. "On the cold fall nights, our pets were smuggled into hotel rooms under long overcoats," George Burr recalled in a 1982 article (2).

While George Burr had the appointment at the university, funding was so tight that Mildred volunteered to help with the work (3). The Burrs felt that, if they were to make any headway with this nutritional syndrome, they had to exclude fats more rigorously from the simple diet and had to quantify the symptoms of the deficiency as thoroughly as possible. This way, they would be able to measure the relative curative properties of additives they put in the simple diet later on.

In the 1929 JBC paper, the Burrs described the new nutrition deficiency in detail. When fats were eliminated from the diet for several months but the amount of food wasn't changed, the rats developed scaly skin. Their tails became inflamed and soon ridged with scales. The hind paws reddened and sometimes swelled. The fur on the back filled with dandruff. The animals lost fur around the face and throat with sores appearing. As they continued on the fat-free diet, the animals began to lose weight and, within three or four months of the weight loss, died. When they were autopsied, the Burrs noted that the animals' kidneys and urinary tracts bore significant signs of damage. The Burrs showed that added vitamins didn't help the animals recover from the syndrome, but adding small amounts of lard, as little as three drops, was enough to help the animal recover.

At this stage, the Burrs could conclude only that fat starvation over a period of several months caused a disease in rats that eventually led to death. They didn't know if the rats died because of the strain of having to synthesize fats internally or because of the missing fats from the diet.

But the second paper, which appeared the next year, put the question to rest. The Burrs showed that linoleic acid was an essential fatty acid that was needed in only small amounts to support health. Their work "led them to identify polyunsaturated fatty acids" as essential nutrients, explains William Smith at the University of Michigan, Ann Arbor.

The Burrs established that the fat-deprived rats could not be cured with saturated fatty acids, such as stearic, palmitic and lauric acids. But if the rats were given linoleic acid from sources such as olive oil, lard or linseed oil, they were cured. The Burrs went on to show that complex, unsaturated oils like corn or cod liver oils were better at curing the animals than just a single fatty acid or phospholipid. They had to use physical and chemical means of separation to analyze the components of the fats, because their work preceded the days of common analytical techniques such as thin-layer and gas chromatography, spectroscopy, and automatic fractionating methods.

"In a little while, we had an extreme deficiency in our young animals," Burr said in the 1980 speech. "We had run our first fat deficiency experiment and didn't know it."

Their findings were "born into controversy" wrote Ralph Holman of the Hormel Institute in 1998 (3). In the 1940s, Holman was one of George Burr's graduate students and later a research associate. Holman pointed out that in the same issue of the JBC as the second paper, a group led by Lafayette Mendel at Yale University had a paper that concluded that fat's nutritional value was solely in fat-soluble vitamins and calories but not fatty acids (4). In his 1982 article, George Burr remembered receiving a letter of condolence for coming to the conclusion that fatty acids were important (2).

Later work, some of it done by Holman, went on to demonstrate that linoleic acid was critical in the human diet (5, 6). As more research gave credence to the Burrs' work, a different mindset took hold that went to the other extreme. Nutritionists believed that linoleic acid was the only essential fatty acid. "The idea that linoleic acid was the essential fatty acid persisted for a long time, even into the 1990s," says Salem. He adds the thinking was so pervasive that linoleic acid was the only fatty acid required to be added to infant formula. It was only in the mid-1990s that the World Health Organization "said infant formula should have a fatty acid distribution more like human milk, which contained other long-chain, polyunsaturated fatty acids as well," says Salem, citing the omega-3 and omega-6 fatty acids DHA and arachidonic acid as examples.

Salem says that modern nutritional biochemists can learn a lesson from the Burrs' experimental procedures. By keeping the diet very simple and repurifying the proteins and sugars, the Burrs "invented the whole approach of how to exclude fat from the diet. It is a mistake people still make today," he says. Salem explains that researchers get waylaid by the description "fat free" in a product catalog, not realizing the product may have traces of fat still in it. The Burrs did not take those risks. They went to great lengths to make sure that all the materials they were using to design the diet were truly devoid of any traces of fat.

The skin symptoms in the Burrs' rats were striking. It is only now that some understanding of how linoleic acid plays a role in maintaining healthy skin is starting to emerge. In a recent JBC publication, recognized as one of the "Best of JBC 2011" papers, Alan Brash's group at Vanderbilt University proposed an explanation for the critical role of linoleic acid in building the water barrier in the skin (7). Brash says that the Burrs noted that the fat-deprived rats lost more water through their scaly skin. By using a series of analytical techniques, Brash's group demonstrated that two particular lipoxygenases are responsible for oxidizing linoleic acid esterified in a special ceramide to allow the subsequent covalent bonding of epidermal proteins and ceramides together to produce a functional barrier to water loss.

Mildred Burr died in 1962. George Burr's career later took him to Hawaii and Taiwan, working on photosynthesis in agricultural crops. Burr was the first to discover that sugarcane used C4 carbon fixation. He died in 1990.

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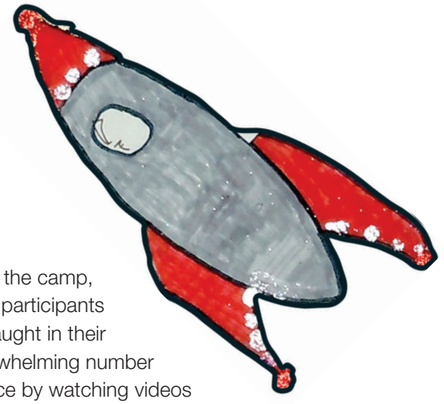
The kids agree: Camp BlastOff! was a blast



BY MICHAEL R. NELSON, NINA MARTIN, JONATHAN MERRITT AND JAMES T. HAZZARD

Over the summer, the University of Arizona's Undergraduate Affiliate Network chapter and biochemistry club hosted their first multidisciplinary BlastOff! Summer Science Camp, which aimed to provide 15 Tucson middle-school students from historically underrepresented ethnic groups and students with limited exposure to science with the opportunity to engage in hands-on scientific experiments.

Developed around the theme of outer-space exploration, BlastOff! covered topics from the fields of physics, engineering, molecular biology and biochemistry. The activities challenged students' problem-solving abilities and their understanding of scientific topics.

The campers explored the chemistry of soil testing and water purification, learned about the importance of light for life on Earth, identified an organism using DNA-fingerprinting techniques (students isolated their own DNA), and built their own solar-powered vehicles and "rocket ships" with baking soda and vinegar. The students also took field trips to the university's Flandrau Planetarium and the Steward Observatory Mirror Lab, which was about to begin casting the Giant Magellan Telescope mirror for use at Las Campanas Observatory in Chile. Meanwhile, Carol Dieckmann, a professor in the molecular and cellular biology department, gave a highly entertaining and educational presentation about the green alga Chlamydomonas and how it controls phototaxis by using its large eye spot and flagella.

On the closing morning of the camp, students engaged in a "CSI"-like investigation attempting to identify who murdered a space alien by analyzing DNA samples on an agarose gel. In the afternoon, siblings, parents and other family members watched a bottle-rocket launching contest, a solar-powered car race and a strongest-spaghetti-bridge contest and viewed posters made by the camp teams. The week closed with an award ceremony in which all the campers were declared winners.

During the course of the camp, several of us asked the participants about how science is taught in their schools. Sadly, an overwhelming number said they learned science by watching videos in the classroom; only two out of the 15 said they had ever taken field trips! Therefore, it was very rewarding to read the campers' (sometimes humorous) comments about the camp.

Team ACEISSO: (from left) Isela, Sarina, Carolina, Angelica (UA), Shiana (UA) and Eddie (UA)

Team Marvelous Martians: (from left) Bottle rocket contest winners Vanessa and Neyda

• Madison Cruz–Lewis wrote: "My favorite activity was harvesting our own DNA. This activity was kind of disgusting because we had to put saltwater in our mouths, but in the end it was cool to see our DNA!!"
• Rashell Pedrego noted: "I really enjoyed making The Slime [a mixture of borax, glue, water and food coloring]. It was cool how Yurika and I made seven times the amount of Slime than anyone else."
• Vanessa Villalobos' comments well summarized all the campers' impressions: "I had a wonderful time at BlastOff … I learned a lot about science in a fun way, like how to make a rocket and a solar-powered car. It was a great experience."
• Villalobos' older sister, Isela, looking to the future, said: "BlastOff was an experience I will never forget. I was able to meet other kids and have a great time conducting experiments and listening to presentations. I hope to come back next year as a Junior Leader."

It was very gratifying that a large number of the UA students who served as team leaders said they were committed to working on the second BlastOff! camp next summer despite the great deal of time and energy required. We have begun developing a modified curriculum that will incorporate more field trips and perhaps a more biological theme. Both the middle-school and undergraduate participants overwhelmingly felt the camp was a great success and a lot of fun, and that is, after all, what science should be!

FINANCIAL SUPPORT

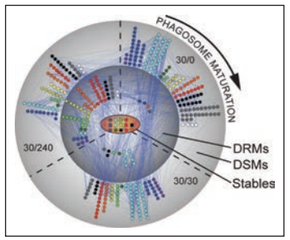
We were very fortunate to obtain substantial financial support from a variety of sources:

- For initial planning in the summer of 2011, we obtained an Outreach Support Award from the UAN.
- Last fall and winter, we obtained funds from various university departments, colleges, offices and faculty members, including Marc Tischler and James T. Hazzard, which went toward the purchase of materials, equipment, snacks and refreshments.
- Lunches were donated by Tucson-area eateries.

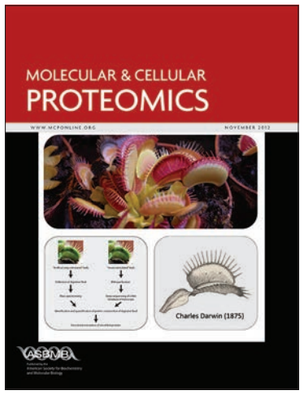
MCP MOLECULAR & CELLULAR PROTEOMICS

A dynamic view of phagocytosis

BY RAJENDRANI MUKHOPADHYAY



Cells use a process called phagocytosis to capture and degrade large particles, such as microorganisms, inside special packages. These special packages, called phagosomes, pinch off the cellular plasma membrane and are dynamic entities that mature inside cells as they break down their contents. But how do the membranes of phagosomes arrange themselves during the process? Some studies have hinted that phagosomes' membranes may contain lipid rafts, which are microdomains initially thought to be unique to the plasma membrane. In a recent Molecular & Cellular Proteomics paper, Michel Desjardins at the University of Montreal in Canada and colleagues used both proteomics and bioinformatics to carry out a large-scale characterization of the spatiotemporal changes that occurred during three stages of the phagosomal maturation process, focusing on the proteins associated with lipid rafts (1). They saw that the membrane microdomains in phagosomes assembled late in the maturation process. The finding was surprising to the investigators, as they expected the microdomains to be acquired early from the plasma membrane, where these structures are enriched and well organized, explains Desjardins. The investigators went on to find that many of the proteins within microdomains at later stages were indeed present in less mature phagosomes but were found in other parts of the membrane. Desjardins explains that the data indicate the membrane is actively reorganized to assemble the lipid rafts during phagosome maturation. He adds that one future direction of the study will be to investigate how pathogens like Leishmania, Brucella and Mycobacterium can disrupt the formation of lipid rafts to inhibit the phagocytotic process.



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jbc THE JOURNAL OF BIOLOGICAL CHEMISTRY

Oncogenic phosphatase disrupts placental development

BY RAJENDRANI MUKHOPADHYAY

In mammals, the placenta is the lifeline between a mother and her unborn offspring. In a recent Paper of the Week in The Journal of Biological Chemistry, researchers demonstrated that mutations in an unusual class of phosphatases disrupted development of the placenta in mice. The phosphatases were the PRL phosphatases. "Unlike most protein phosphatases that counteract the activity of protein kinases, the PRLs play a positive role in signaling," says Zhong-Yin Zhang at the Indiana University School of Medicine. Mutations in these phosphatases have been linked to a number of different cancers, such as those that develop in the colon, pancreas, breast and lung. Despite a wealth of data obtained in cultured cells while looking at the roles for PRLs in cell growth in organs like the placenta and metastasis, their molecular mechanisms remain a mystery. So Zhang and his colleagues deleted the most ubiquitously expressed PRL family member, PRL2, in mice. They found that the deletion disrupted placental development and interfered with the growth of embryonic and adult mice. The investigators established that PRL2 promotes placental development — and potentially cancer, when it goes awry — by targeting the tumor suppressor PTEN for degradation in the proteasome. PTEN's function is to deactivate Akt, a master kinase involved in the regulation of cell growth and survival. Therefore, when PRL2 removes PTEN from the scene, Akt springs into action and allows cells to proliferate. For this reason, Zhang says, PRL2, when mutated, qualifies as an oncogene and may be an attractive target for anticancer drug design.

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From snail snatching to medical modulations

One man's auspicious blend of past experience and present skills yields future success

BY ERICA M. SHARPE

Priceless explorations and explanations of DNA exonuclease processivity and the discovery of conotoxins make this man a valued contributor to both enzymology and neuroscience. However, he remarkably discovered the latter using little to no expensive laboratory equipment. Faced by lack of funding in the Philippines, where he returned home to work, he called on his own ingenuity to develop and complete what would be a monumental study. The subject of said study was a very simple and readily accessible resource in his part of the world: snail venom. This man is Baldomero Olivera, and two of his papers are now recognized as Journal of Biological Chemistry "Classics."

Olivera's venom explorations proved fruitful when, after much hard work, he discovered conotoxins, the material discussed in one of the two articles highlighted in the JBC (1) and the material that would have a huge impact in the fields of neurology and medicine.

Remembering his pastime of collecting snails as a child, and having inside knowledge in the field of DNA enzymology, Olivera knew the potential value of carrying out a systematic study on the venom found in cone snails. Using his keen analytical, biophysical, enzymological and laboratory skills as well as his aptitude for gathering gastropods, he successfully isolated and purified the active peptides in cone snail venom. He named these venom peptides conotoxins, and their discovery led to the creation of an entirely new field of research.

These toxins target sodium and calcium channels in the body. At the time of their discovery, little was known about voltage-gated calcium channels, which are present in excitable cells, such as muscle cells and neurons, and which initiate contraction or excitation, respectively, upon the passage of calcium through the channels. One of Olivera's peptides from cone snails, the ω-conotoxin GVIA, functions through inhibition of calcium uptake through binding to neuronal calcium channels. News of this discovery caused a boon of research in this field, yielding more than 2,000 studies that utilized Olivera's synthesized version of the ω-GVIA peptide, active at concentrations of less than 1E-12M! Research in this field finally resulted in the purification of the neuronal calcium channel, which was subsequently named "the conotoxin receptor" after Olivera's peptide. In addition to the impact this discovery had in the field of neuroscience, a conotoxin peptide has been approved as a painkiller with strength exceeding that of morphine.

Young scientists should note that these successes were not merely a chance happening. Olivera had performed significant work in the field of DNA exonuclease enzymology, using radioactive tagging of DNA to study the processivity of eight different enzymes. This work was published before restriction enzymes were used and far before genome sequencing took the stage. The second "Classic" presented in the JBC reports his discoveries in the field of DNA processivity in a time when this concept was unheard of (2).

Children radiate curiosity and the desire to discover the world around them. Many successful scientists like Olivera never lose grip of that youthful curiosity and adventurous spirit, allowing them to draw on experiences and creative ventures in childhood to inspire their current research pursuits. Motivated by their successes, I'd like to encourage all aspiring scientists to nurture this childlike curiosity and to take Olivera's example: Create continuity between your past and present selves, the adventurous child inside and the professional adult you are working to become. You may discover that with a youthful, exploratory attitude, you break through obstacles and create and discover things you never dared to imagine.

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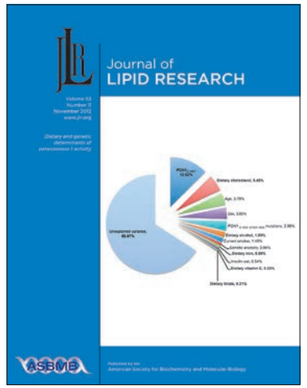
THE JOURNAL OF LIPID RESEARCH

Human cholesterol transporter in mice

Investigating behavior of NPC1L1 expressed in the mouse liver

BY MARY L. CHANG



The cholesterol transporter Niemann–Pick C1-like protein, or NPC1L1, efficiently absorbs cholesterol in the small intestine. The popular drug ezetimibe, marketed under the trade name Zetia, blocks function of this transporter, effectively lowering cholesterol levels, especially that of low-density lipoprotein. While NPC1L1 is found in abundance in the human liver, its relationship with liver-related cholesterol has not been clear. Another problem is that NPC1L1 is not present in the liver of mice, the primary animal model for NPC1L1 studies.

In a commentary appearing in the November issue of the Journal of Lipid Research, Philip N. Howles and editorial board member David Y. Hui of the University of Cincinnati College of Medicine discuss the findings presented in "Modulation of lipid metabolism with the overexpression of NPC1L1" by Makoto Kurano and colleagues at the University of Tokyo. Utilizing adenovirus-mediated gene-transfer technology, human NPC1L1 was overexpressed in mouse liver, and the effects of this overexpression were examined in mice fed normal diets with or without ezetimibe.

As should be expected, the expression of NPC1L1 in the liver led to increased intrahepatic cholesterol as the efficiency of cholesterol absorption increased there. But there were two results that weren't expected. Apolipoprotein E-rich lipoprotein was found in plasma, indicating there was increased uptake of cholesterol from bile, as overexpressed NPC1L1 was discovered to be located near channels of bile ducts. And VLDL triglyceride content decreased, explained by the authors as possibly being affected either by stress on the endoplasmic reticulum of liver cells or by the suppression of expression of the forkhead box protein O1 gene, known as FoxO1, directly by the overexpression of NPC1L1. Treatment with ezetimibe made minimal difference to these effects.

While there are significant differences between a mouse and a human — including the mouse's lack of cholesteryl ester transfer protein, which plays a major role in lipoprotein metabolism in most mammals — this study and others point to NPC1L1 in the liver as having important functions not yet discovered.

Mary L. Chang (mchang@asbmb.org) is managing editor of the Journal of Lipid Research and coordinating journal manager of Molecular and Cellular Proteomics.

Look at an exam, see a job application

Preparing students for real-world questions

BY PETER J. KENNELLY

How many times has this happened to you?

Question (2 points):
Name two intermediates of the tricarboxylic, a.k.a. Krebs, cycle.

Answer: Isocitrate, fumarate, malonyl-CoA

1 point

Instructor's comment: Isocitrate and fumarate are intermediates in the Krebs cycle, but malonyl-CoA is not. Two correct minus one incorrect response yields one net correct response.

Student's response: Why didn't I get both points? I listed two correct intermediates, so the third one shouldn't count.

Question (5 points):
In the space provided, describe the molecular attributes of ethidium bromide that contribute to its ability to intercalate double-stranded DNA.

Answer: Ethidium bromide resembles a nucleotide base.

2 points

Instructor's comment: While your statement is correct, you need to be more specific. For example, you might have explained how the planar shape, hydrophobicity and pi electron clouds on ethidium bromide contribute to its capacity to bind DNA.

Student's response: That's what I meant. In class you said, "Ethidium bromide resembles a nucleotides base." I've got it written in my notes. I don't understand why you didn't give me more points.

Question (2 points):
Draw the structure of any amino acid containing a hydrophobic side chain:

Answer: Phenylalanine

0 points

Instructor's comment: The question asked you to draw a structure.

Student's response: But phenylalanine has a hydrophobic side chain. I deserve partial credit.

Everybody's doing it

Many college students have learned that if they simply persist long enough in pressing their cases, a reasonable chance exists that they can wear down instructors until they concede a few more points. There are a number of ways that instructors deal with the segment of the student population for whom negotiating with the instructor has become a cornerstone of their strategy for academic success. Some avoid questions of this type, perhaps by relying exclusively on the multiple-choice format. Some simply award points for the mention of key words and phrases, ignoring whether the dots were connected correctly, the presence of incorrect information or statements, or failure to adhere to the directions given.

If you are an instructor who chooses to reward students whose answers are concise, correct and cogent, more likely than not you will encounter the argument that you are an outlier. A handful of students will protest that no other instructor includes the quality of overall construction of a response into his or her scoring rubric. Some students may plead that they don't know how to answer your questions and ask what you are looking for with the expectation that you will reveal some secret formula. One or more may state with complete sincerity that they never have experienced difficulties in other classes. Unfortunately, all too often a look at their transcripts will bear out this claim.

This may sting a little

In the blink of an eye, today's students will be filling out job applications rather than pop quizzes. They will be questioned during interviews. Both the substance and form of their responses will determine whether they will be able to gain admission to graduate or professional schools or employment and advancement in their chosen professions. One can justifiably argue that it is beyond the purview of today's overburdened college faculty to take on the task of helping students learn how to answer questions effectively. However, we should also do our best to avoid practices that reward and reinforce poor question-answering skills.

While college classrooms are populated by many bright and self-motivated students, they also usually contain some whose focus is strictly on doing what is necessary to acquire a target grade. For these students, points are the only real motivator. Thus, if instructors award full credit for simply mentioning the right words or phrases, they provide little incentive for students to learn how to frame succinct, direct responses. Those students who habitually respond with disjointed rambles that include anything peripherally associated with the question probably will continue to do so regardless of any qualitative feedback the instructor may provide. If we give full credit to students who provide more responses than requested, there is no incentive for them to develop the depth of understanding and analytical skill needed to make and commit to a specific choice. If a student receives full credit when the instructor can see that the correct answer is "in there somewhere," there is little incentive to develop a more extensive vocabulary or to do a better job of connecting the dots.

So next time you construct your scoring rubric for short-answer and essay questions, leave a few points to reward students for well-crafted responses and as an inducement to those students who need to develop or refine those skills. Take time when going over the exam in class to provide and analyze examples of responses that illustrate best practices. While some of your students may moan and groan, if you are clear about your rationale and expectations and consistent in your scoring, you may be surprised at the improvement.

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Great graduate school applications: what program directors look for

BY KEVIN MCPHERSON

It's my junior year. I've done all of the tedious, general laboratory classes and taken all the foundational math and physics courses, and I've begun to hunger for more of a challenge, some way that I can apply these topics beyond textbooks and show my love for research: graduate school. But the graduate-school application process can be overwhelming for those of us balancing classes, extracurricular activities and interpersonal relationships, so I decided to go straight to the source to find out how to go about it: the professors who make up the admissions committees at the top research universities in the nation.

My quest to shed light on the enigma that is the application process of Ph.D. and M.D./Ph.D. degree programs was set. The questions I needed to have answered: How the heck do I write a CV? What are the important pieces that make up the application of a worthy Ph.D. or M.D./Ph.D. candidate at a top-notch research university? How is each of those pieces weighed?

The curriculum vitae

One of my biggest concerns going into scientific research was the state of my curriculum vita. I had no point of reference for how to write one, so surely this would be the weakest part of my application. Luckily, Robert Simoni, director of Stanford University's biology Ph.D. program, soothed my fears, explaining that the CV does not hold much importance, "but that is not to say that accomplishments as an undergraduate are not important, as they, of course, are. It is that [these accomplishments] are covered in other parts of the application."

Phew! So no sleepless nights would be spent wondering whether I had the correct citation style on my publications or if the dates on my CV had to go in descending or ascending order. However, the general consensus of the directors I asked was that this part of the application should be well organized and concise, with Simoni emphasizing the importance of being judicious about what you should include. "Don't include papers in preparation or submitted," he said. "Only include papers that have been published or are in press."

Gradually, however, the question of what limits I should set on my CV arose. Simoni said that most scientists have two CVs: a short, National Institutes of Health-style one and a full version.

Should I mention any merits I gained in high school? The opinions on this varied. Simoni said he found high school accomplishments "quite appropriate," while Ronald Koening, director of University of Michigan's M.D./Ph.D. program, said accomplishments that are "college and beyond" are more fitting to a CV.

The key components that make you stand out

So if I'm not biting my nails over how my accomplishments are translated on paper, what would make me a standout applicant?

"The single most important thing are the letters, especially from the research adviser," Simoni told me. "Next is whether the student's interests, usually expressed in the personal statement and list of faculty of interest, match the departmental/program interests."

Skip Brass of University of Pennsylvania's M.D./Ph.D. program said there are four elements that he looks for that make up a successful applicant: "1) academic success, 2) substantial research experience, 3) letters of recommendation from research PIs and 4) a well-articulated [personal statement]." Simoni reinforced that each of these portions of the application tells the applicant's unique story, while adding that, yes, GREs are important too.

Simoni and Brass also debunked the myth about publications as an undergraduate, saying that they are "a bonus" and that "although they are not required, two-thirds of our class have them," respectively.

After interviewing these men of academia, I was a little less anxious about the application process. I knew that most of what was being translated on paper would be a reflection and culmination of my work at my current school. My CV had to look a little less muddled; I had to pick professors to write stellar recommendations; and, most importantly, I had to figure out why I wanted to do research (and tell it in a compelling way). Not bad – the whole process was working itself out to be a simple, little recipe. It felt like a weight had been lifted off my shoulders. It was so simple to obtain this information: Most of the people I asked questions of were candid and elaborated on the process. This is not surprising, but it is refreshing to me as I move forward in science.

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Levuglandins

Finding lipid superglue in vivo

BY ROBERT G. SALOMON

Curiosity-driven basic research on the chemistry of PGH2, the endoperoxide intermediate in the biosynthesis of prostaglandins, uncovered a novel nonenzymatic rearrangement that produces levulinic aldehyde derivatives with prostanoid side chains that we named levuglandins, LGE2 and LGD2 (1). Detecting these oxidized lipids in vivo is complicated by their proclivity to stick like superglue to proteins within seconds. They form pyrroles that incorporate the ε-amino group of lysyl residues and generate DNA–protein or protein–protein crosslinks within minutes.

Detecting LG adducts in vivo

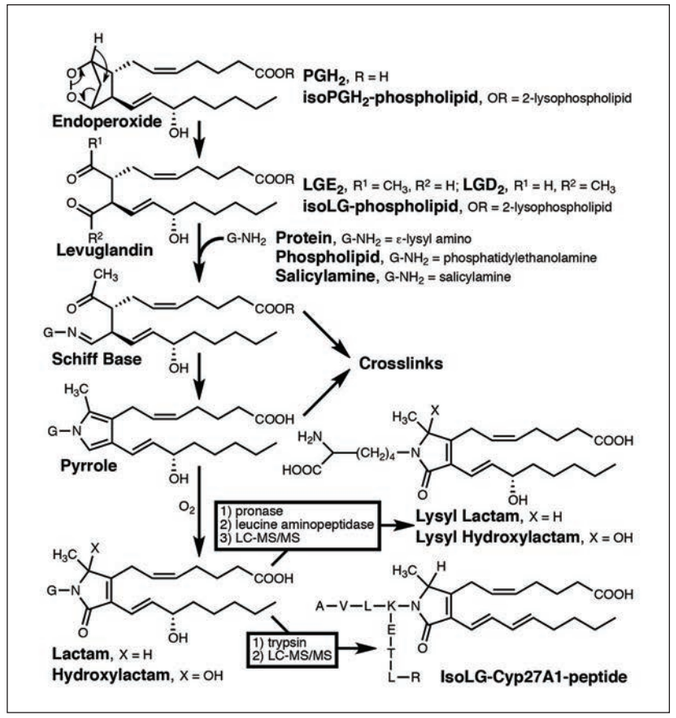
Immunoassays with antibodies raised against protein adducts of LGs generated by chemical synthesis provided evidence for their presence in human and mouse blood and tissues and enabled our discovery that free-radical-induced oxidation of arachidonyl phospholipids in low-density lipoprotein generates LGE2 (2) as well as isomers named isolevuglandins (3). Total LG/isoLG-adduct levels in vivo can be measured by exhaustive proteolysis and liquid chromatography–mass spectrometry quantitation of the excised LG-modified lysine (4). MS analysis revealed that the adducts are mainly lactams and hydroxylactams generated by oxidation of the initial pyrrole adducts (4). LC–MS/MS analysis also detected isoLG-phosphatidylethanolamine adducts in human blood and mouse liver (5).

IsoLG-protein adducts are markers of cumulative oxidative injury

A murine Candida sepsis model of inflammation exhibited a 3.5-fold increase in adducts of plasma proteins after pathogen exposure (6). Unlike lipid markers (e.g., isoprostanes), which are rapidly cleared from the circulation, isoLG-protein adducts accumulate. Therefore, like a dosimeter, they provide a cumulative index of oxidative injury. Elevated levels of LGs/isoLGs are found in various disease conditions linked with oxidative stress and inflammation.

Salicylamines selectively trap LGs/isoLGs in vivo

A search for sacrificial primary amines that efficiently trap LGs/isoLGs led to the discovery that ortho-hydroxy benzylamines, salicylamines, are uniquely reactive toward these γ-ketoaldehydes, apparently because the ortho hydroxyl group catalyzes cyclization of an unstable intermediate Schiff base adduct to a pyrrole. By selectively trapping LGs/isoLGs, salicylamines can prevent protein modification in vivo (7). This provides a useful tool for assessing the involvement of LGs/isoLGs in pathology and is a starting point for the development of drugs that neutralize these toxic oxidized lipids.



Generation of LGs/isoLGs and their adducts with proteins, phosphatidylethanolamine, and salicylamine.

Characterizing in vivo LG/isoLG modification of specific proteins

The effects of LG/isoLG-protein adduction on protein or cellular function can be studied conveniently in vitro (8). However, understanding the pathological significance of those effects requires knowledge of the specific proteins affected and their levels of modification in disease states. Last year, the detection and characterization of LG/isoLG-protein adducts took a quantum leap forward with the development of LC–MS/MS technology that identified the sites of modification, e.g., the isoLG-modified tryptic peptide AVLKETLR in a mitochondrial protein, Cyp27A1, extracted from human retina (9).

LGs and isoLGs are among the most potent naturally occurring crosslinking agents. The remaining challenges for understanding the biological significance of LGs and isoLGs include characterizing the structures and biological consequences of LG/isoLG-induced crosslinking. Protein–protein crosslinks may contribute to the disease-related formation and accumulation of protein aggregates. DNA–protein crosslinks could influence gene expression under conditions of oxidative stress.

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The 2012 Nobel Prize in Chemistry on Twitter

Any time biochemists win the Nobel Prize in Chemistry, chemists start asking what exactly it means to be a chemist. Here's a snapshot of how this year's prize to Robert Lefkowitz and Brian Kobilka for G-protein–coupled receptors played out on Twitter. Read more at science writer Rajendrani Mukhopadhyay's blog, **www.wildtypes.wordpress.com**

@heppnerd: Happy to see Biochemists winning #NobelPrizes in #Chemistry. Need to gray the lines between disciplines to make largest impacts. #GPCRs

@sciencegeist: It's a collective action problem between "us" and the Nobel Medicine folks. You get 3 bullets max to fire, once a year.

@Chemjobber: @sciencegeist Who's going to share their pie w/the biologists? Apparently, it's the chemists. #ChemNobelGrumpyPants

@SeeArrOh: @sciencegeist @stuartcantrill @Chemjobber – Problem for me is the reverse: Why don't more chemists win for Med, Physics, Lasker, etc? (2/2)

@sciencegeist: @SeeArrOh @stuartcantrill @Chemjobber 2C) Are we just getting our collective panties in a bunch over this?

@stuartcantrill: 'No' RT @Chemjobber: @sciencegeist Question: if we asked Lefkowitz/Kobilka "are you chemists?" What do you think their answer would be?

@tonzani: @stuartcantrill @Chemjobber @sciencegeist Probably "No, thank God, otherwise we wouldn't have won the Nobel Prize"?

@RajMukhop: And as arguments begin over whether biochemists are chemists, check out my 2009 story on the chem #Nobelprize

Reader comments

Service is in our best self-interest, September 2012

I have to agree wholeheartedly with Tom Baldwin's suggestions for not only increasing our commitment to community outreach but also that departments and university administrators take our efforts seriously. Frankly, I believe the former is much easier to achieve than the latter. As a friend of mine (a devoted member of the American Society for Biochemistry and Molecular Biology, the Undergraduate Affiliate Network and the Education and Professional Development Committee) once put it, "With heavy teaching loads, the need to do research and apply for grants, as well as sit on numerous committees, where am I going to find the time?" One problem that exists in the academic circles is the definition of outreach, which is supposedly part of every faculty member's obligation. All too often, outreach means serving on departmental and university committees rather than interaction with the nonuniversity community.

A very easy mechanism by which our departments and universities can increase their impact on their local communities is by the establishment and support of UAN chapters on their campuses. Baldwin was instrumental in the inclusion of our university's Biochemistry Club in the UAN in the mid-2000s. Though it took a while for our UAN chapter to establish an identity and a mission, we have now developed three strong community outreach activities, two of which have been or will be highlighted in ASBMB Today. These activities consist of an undergraduate research conference, to which are invited high school students engaged in research on our campus; our Visiting Scholars Program, in which our UAN members visit local high schools to talk about their research and give advice on preparing for and surviving the college experience; and a multidisciplinary middle school summer science camp targeting schools with predominately Hispanic and Native American populations. Our UAN chapter is far from being unique in these endeavors; most chapters have similar strong outreach activities in which they are acting as excellent role models and ambassadors for ASBMB and science. The society as a whole is indeed very lucky to have these energetic and enthusiastic young people spreading the message in our communities, although all too often the membership of ASBMB is unaware of these activities. In fact, a brief glimpse at the UAN chapter map (http://www.asbmb.org/Page.aspx?id=2376) will reveal that there are only about 60 chapters for the entire nation, a rather paltry number considering the number of universities and colleges represented by our general membership. Therefore, if faculty members are seriously interested in making an impact on their local communities, establish and nurture a fledgling UAN chapter (contact Weiyi Zhao, wzhao@asbmb.org) and then let the undergraduates develop their own individualized outreach activities.

– JAMES T. HAZZARD, UNIVERSITY OF ARIZONA

Boston

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RNA Function and Protein Synthesis

Transitions, Education and Professional Development

Triple Negative Breast Cancer

SPECIAL EVENTS

Professional Development for Graduate/Postdoctoral Trainees
Saturday, April 20

ASBMB Opening Reception
Saturday, April 20, immediately follows the Opening Lecture

Undergraduate Orientation: A Student's Guide to the ASBMB Annual Meeting
Saturday, April 20

17th Annual Undergraduate Student Research Poster Competition
Saturday, April 20

Beyond College: Coping with Some Common Challenges
Undergraduate workshop, Saturday, April 20

Undergraduate Breakfast with ASBMB Award Winners
Sunday, April 21, and Monday, April 22

ASBMB Welcome and Networking Reception
Sunday, April 21

ASBMB Thematic Fermentation Happy Hour
Monday, April 22

ASBMB Women Scientists Networking Event
Tuesday, April 23

Y.E.S. Mixer (Young Experimental Scientists)
Consult program for details